
Letters

ASYMPTOMATIC LONG-STANDING PANHYPOGAMMAGLOBULINEMIA WITH IMPAIRED ANTIBODY RESPONSES

Panhypogammaglobulinemia is the serologic hallmark of common variable immunodeficiency (CVID), a heterogeneous primary immunodeficiency syndrome.¹ Although rare (incidence, 1:50,000–1:100,000), CVID represents one of the most common symptomatic humoral immunodeficiency syndromes.² Panhypogammaglobulinemia in CVID is accompanied by impaired antibody responses to vaccines and recurrent sinopulmonary infections, particularly with encapsulated bacteria.³

Early descriptive reports noted that some patients with CVID remain free of infection despite profound hypogammaglobulinemia.³ A recent report⁴ from Spain describes a cohort of patients with hypogammaglobulinemia of unknown duration with autoimmune features but no history of recurrent sinopulmonary infections. We describe 3 patients with profound long-standing hypogammaglobulinemia who did not experience clinically significant bacterial sinopulmonary infections despite ineffective IgG boost responses after vaccination with bacterial vaccines.

The first patient was a 51-year-old man, without a history of sinusitis, pneumonia, or other bacterial infections, who presented for a second opinion regarding a diagnosis of immunodeficiency. Medical records documented panhypogammaglobulinemia in 1997. At presentation, quantitative immunoglobulins revealed an IgG level of 169 mg/dL (reference range, 650–2,000 mg/dL), an IgM level of 25 mg/dL (reference range, 40–270 mg/dL), and an IgA level of less than 8 mg/dL (reference range, 50–100 mg/dL). The serum albumin level was normal, at 4.5 g/dL. Flow cytometry revealed normal numbers of CD3⁺ CD8⁺ T lymphocytes and CD19⁺ B cells and a marginally low CD4⁺ T-lymphocyte count of 461/ μ L (reference range, 560/ μ L–1,840/ μ L). The result of human immunodeficiency virus testing was negative. Prevacination titers against tetanus toxoid were protective (1.2 IU/mL). Prevacination titers against hemophilus influenza B (HIB) and *Streptococcus pneumoniae* were not protective, and 6 weeks after immunization with conjugated HIB and pneumococcal vaccine polyvalent (Pneumovax 23), titers failed to increase. The result of the computed tomographic (CT) scan of the chest was normal.

The second patient was a 25-year-old woman who had markedly reduced serum globulin (1.6 g/dL; reference range, 2.5–3.0 g/dL) during routine evaluation at the age of 15 years. Ten years later, the patient was reevaluated and had profound panhypogammaglobulinemia. Her medical history was devoid of sinopulmonary infections. On referral, she had a

serum IgG level of 81 mg/dL (reference range, 650–2,000 mg/dL), an IgM level of 10 mg/dL (reference range, 40–270 mg/dL), and an IgA level of less than 8 mg/dL (reference range, 50–100 mg/dL). Her serum albumin level was normal, at 4.5 g/dL. Flow cytometry revealed normal numbers of CD3⁺ CD4⁺ and CD3⁺ CD8⁺ T lymphocytes and CD19⁺ B cells. Prevacination antibody titers against HIB and tetanus toxoid were protective, whereas *S pneumoniae* titers were nonprotective. There was no increase in antibody titers after vaccination with pneumococcal vaccine polyvalent. The result of a CT scan of the chest was unremarkable.

The third patient was a 46-year-old man with a history significant for idiopathic thrombocytopenia who was found to be hypogammaglobulinemic. Review of hospital records from 1989 revealed hypogammaglobulinemia; however, the patient denied any history of recurrent sinopulmonary infections. Serum immunoglobulin values in 1989 were as follows: IgG, 419 mg/dL (reference range, 650–2,000 mg/dL); IgM, 54 mg/dL (reference range, 40–270 mg/dL); and IgA, 49 mg/dL (reference range, 50–100 mg/dL). A subsequent evaluation in 2003 revealed an IgG level of 57 mg/dL (reference range, 650–2,000 mg/dL); an IgM level of 18 mg/dL (reference range, 40–270 mg/dL); and an IgA level of less than 8 mg/dL (reference range, 50–100 mg/dL). His serum albumin level was normal, at 4.1 g/dL, and flow cytometry revealed normal levels of CD3⁺ CD4⁺ and CD3⁺ CD8⁺ T lymphocytes and CD19⁺ B cells. Antibody titers against tetanus toxoid (0.04 IU/mL), HIB (0.01 IU/mL), and 12 *S pneumoniae* serotypes were nonprotective. There was no increase in antibody titers against any vaccine component 6 weeks after vaccination. The result of a CT scan of the chest revealed innumerable centrilobular nodules throughout both lungs but no bronchiectasis.

The 3 described patients presented with severe panhypogammaglobulinemia of long-standing duration with deficiency of at least 2 immunoglobulin classes (including IgG), decreasing 2 SDs below normal, and with absent polysaccharide antigen responses. Given the fact that these observations were unrelated to protein loss or other conditions associated with hypogammaglobulinemia, we have chosen to diagnose these patients as having CVID. Patients with CVID typically present with recurrent upper and lower respiratory tract infections;⁵ however, other presentations may include granulomatous disease,⁶ autoimmune processes, and lymphoproliferative disorders.⁷

Despite laboratory evidence of humoral immunodeficiency, these patients retained the ability to fight off bacterial sinopulmonary infections. One possible explanation is that these individuals possess an enhanced component of innate immunity (ie, alternative complement system, mannose-binding lectins, toll-like receptors, and defensins) that provides

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protection against bacterial pathogens and compensates for B-cell dysfunction.

In summary, CVID is a heterogeneous immunodeficiency syndrome that spans a broad clinical spectrum. A small subset of patients with a presumptive diagnosis of CVID is spared recurrent infections despite hypogammaglobulinemia and impaired antibody responses to vaccines. Identification and registry of these patients will lead to broader awareness of CVID and will offer an opportunity to study potential innate mechanisms harnessed by the immune system to compensate for cognate defects.

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THE PANCAKE SYNDROME (ORAL MITE ANAPHYLAXIS) BY INGESTION AND INHALATION IN A 52-YEAR-OLD WOMAN IN THE NORTHEASTERN UNITED STATES

Oral anaphylaxis to ingested mites is a severe and potentially life-threatening reaction that has been reported primarily in semitropical and tropical climates. We describe a patient from the northeastern United States who experienced anaphylaxis on 2 separate occasions after ingesting and inhaling

cooking vapors from a commercial pancake mix contaminated with the house dust mite *Dermatophagoides farinae*. The diagnosis was made by visual inspection of and skin testing with the pancake mix.

A 52-year-old female resident of Danvers, Massachusetts, experienced her first episode of eye swelling and lip tingling shortly after eating pancakes made from a buttermilk pancake mix (Krusteaz Pancake Mix; Continental Mills, Seattle, Washington) that had been stored in her kitchen cabinet for 2 years. This reaction was initially attributed to an unknown environmental allergen, because the patient had a history of allergy to dust mites, pollen, mold, and dander, but no history of food allergy. Three months later, while cooking pancakes from the same mix, she experienced wheezing, diffuse redness, and facial swelling that again required emergency department care. The patient was not aspirin sensitive, but was taking a β -blocker for hypertension.

On allergy evaluation, she had positive skin prick test results (15-mm wheal) to house dust mites (*D farinae* and *Dermatophagoides pteronyssinus*; ALK Labs, Round Rock, Texas) and a 9-mm wheal and a 25-mm flare to the pancake mix. Skin prick test results to wheat were negative, and the patient had no history of problems after eating wheat-based products, including pancakes. Although grossly normal in appearance, microscopic examination of the pancake mix revealed a thriving colony of live mites, easily seen under low power (a video is available at <http://www.annallergy.org>). Larry Arlian, PhD, at Wright State University, Dayton, Ohio, confirmed the species as *D farinae*, and a 2-site monoclonal antibody enzyme-linked immunosorbent assay (Indoor Biotechnologies Inc, Charlottesville, Virginia) measured a Der f1 concentration of 322 $\mu\text{g/g}$ of the pancake mix.

A review article¹ in this journal described relatively few published cases of anaphylaxis from oral mite ingestion. To our knowledge, Erben et al² reported the first case of anaphylaxis to mite-contaminated food in 1993, when they described a 48-year-old house dust mite-allergic man who developed anaphylaxis after eating beignets contaminated with *D farinae*. Blanco et al³ have described patients from Spain and Venezuela, some of whom were aspirin sensitive, who experienced severe allergic reactions, some repeated and life threatening, to foodstuffs that contained high quantities of mites. Because most of their patients reacted to mite-contaminated pancake flour, they labeled this condition the “pancake syndrome.” Other reports^{4–6} describe additional cases of anaphylaxis after the ingestion of grains contaminated with mites, often storage mites.

In April 2006, a “Dear Abby” letter⁷ described a 14-year-old boy who experienced dyspnea and cyanosis 10 minutes after eating an outdated pancake mix. This letter cited a 2001 publication⁸ by medical examiners from Charleston, South Carolina, that described the death of a 19-year-old asthmatic man after the ingestion of pancakes made from a packaged mix that had been opened and stored in a cabinet for approximately 2 years. Autopsy showed laryngeal edema and hyperinflated lungs with mu-

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cous plugging consistent with an asthma-related death. The pancake mix was analyzed and found to contain 700 CFU of mold per gram of mix. The researchers presented this case as an unusual case of anaphylaxis to mold-contaminated pancake mix in a patient with mold allergy.

However, anaphylactic reactions in mold-allergic patients to molds in fermented foods, such as cheese, dried fruits, yogurt, and wine, are quite rare, if even existent. The term *farinae* (as in *D farinae*) means “wheat,” and wheat products can be used as culture media for mites. High humidity favors the growth not only of mold but also of mites. In our opinion, the “Dear Abby” case and the death of the 19-year-old man in Charleston were more likely because of mites rather than mold in the pancake mix.

The message from our case report and others cited in the literature is that anaphylaxis from oral ingestion of mites—or from inhalation of mite-contaminated grain mixtures—is a severe, potentially lethal, allergic condition that may be frequently undiagnosed. Although the present patient was not aspirin sensitive, her use of a β -blocker may have increased the severity of her reaction. Most previous cases have been reported in tropical and subtropical countries. Our case from the northeastern United States suggests that this problem may be more prevalent in temperate climates than previously recognized. A female dust mite can lay 60 eggs in its 80-day lifetime. With it taking only weeks for a dust mite to reach maturity, contamination of a wheat product with only a few mites can, in conditions of adequate humidity, lead to a thriving culture within months.

Flour-based products should be stored in a refrigerator or freezer after purchase. Allergy specialists should microscopically examine suspected foodstuffs in cases of unexplained or idiopathic anaphylaxis.

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ADOLESCENT PRESENTATION OF X-LINKED LYMPHOPROLIFERATIVE DISEASE

X-linked lymphoproliferative disease (XLP; OMIM 308240) is characterized as a rare immunodeficiency that presents with Epstein-Barr virus (EBV) infection and has an average age of onset of 2.5 years.¹ The molecular characterization of XLP has led to improved and rapid diagnosis and advanced our understanding in immune responses and development. Gene sequencing in patients with XLP has revealed *SAP/SH2D1A* gene (chromosome Xq25 encodes the SAP protein) mutations in 60% of patients.² Recently, X-linked inhibitor-of-apoptosis deficiency has been reported to cause the clinical phenotype of XLP in 3 families.³ Since SAP is expressed in CD8⁺ T cells, a rapid screening test was developed recently for detection of SAP protein by flow cytometry.⁴

The patient was a previously healthy 16-year-old boy who presented with a 2.5-week history of cough, sore throat, and fever. Tonsillar exudates, lymphadenopathy, and a positive Monospot test result were documented. Five days later, he was admitted to a local hospital for dehydration and was treated with intravenous fluids and corticosteroids. After 4 days, he was transferred to a tertiary care hospital because of hepatic failure. On examination, he was febrile and appeared ill. He displayed respiratory distress, ascites, hepatosplenomegaly, jaundice, and generalized lymphadenopathy. The patient developed respiratory distress that required assisted ventilation and coagulopathy. He was treated with antibiotics, ganciclovir, and intravenous immunoglobulin. The patient had no history of recurrent infections, autoimmune disease, or prior known EBV infection. The family history was unremarkable in first-degree relatives, but a maternal great-uncle died at the age of 9 years of uncharacterized meningoencephalitis and pneumonia (Fig 1A).

EBV titers indicated an acute infection (EBV early antigen, EBV viral capsid antigen IgG, and EBV viral capsid antigen IgM positive and EBV nuclear antigen IgG negative). Polymerase chain reaction for EBV demonstrated 529,500 copies/mL. Immunoglobulin levels were polyclonally elevated, and flow cytometry from the peripheral blood demonstrated elevated B-cell counts and an inverted CD4⁺/CD8⁺ T-cell ratio of 0.7.

On the third day of hospitalization, while awaiting liver transplantation, the patient developed pulmonary hemorrhage that failed to respond to aggressive intervention. The patient's course deteriorated rapidly and a cardiopulmonary arrest ensued. Resuscitative efforts were withheld according to the family's request and the patient died.

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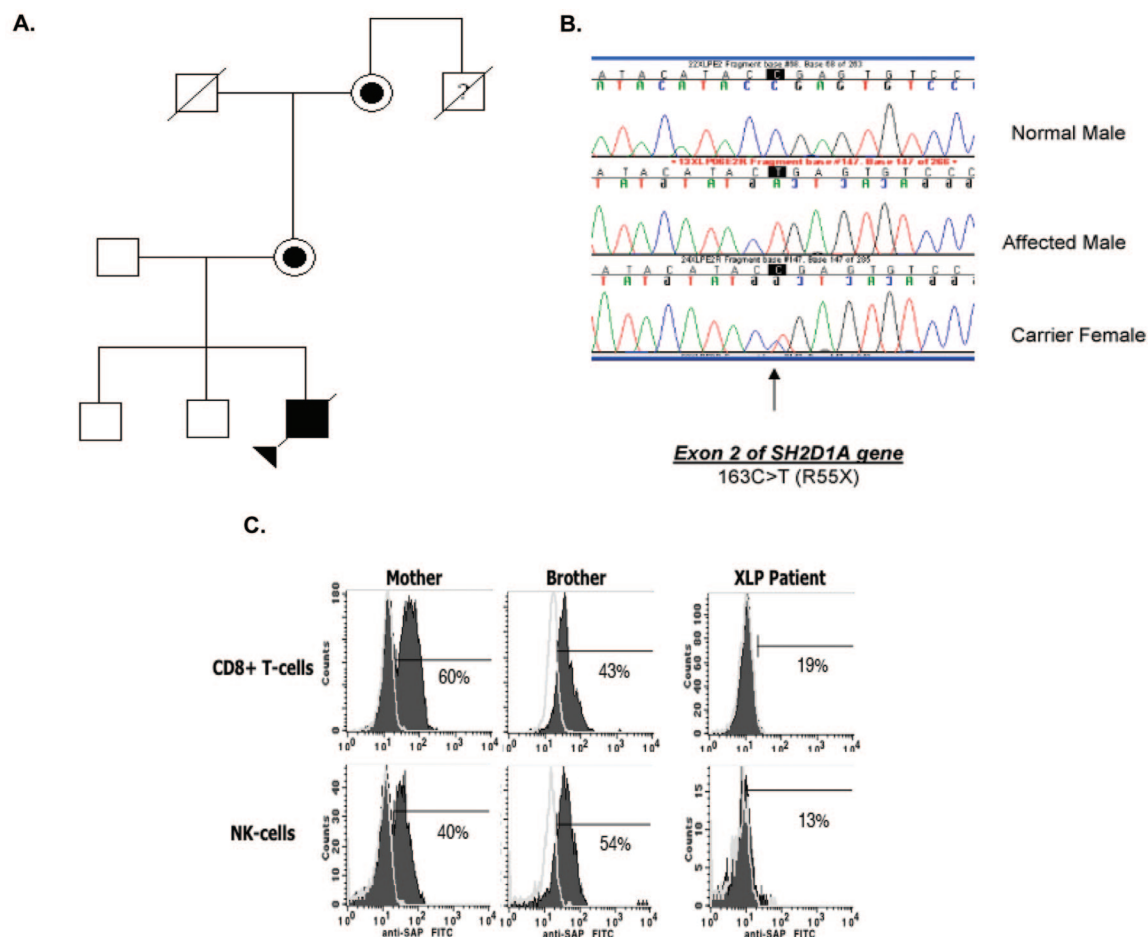


Figure 1. A, Pedigree demonstrating deceased (diagonal line) child affected with X-linked lymphoproliferative disease (XLP) (black square), carrier status (dotted circles) in his mother and maternal grandmother, and possible XLP (question mark) in his maternal great-uncle who died of uncharacterized meningoencephalitis and pneumonia suspected to be due to Epstein-Barr virus. B, DNA sequences revealing a nonsense mutation in exon 2 of the *SH2D1A* gene indicated by a base substitution of a thymine for a cytosine at nucleic acid position 163. This resulted in a premature stop codon R55X during translation of SAP. The proband was hemizygous, the mother was a heterozygous carrier, and the nonaffected brother showed the wild-type sequence. C, SAP expression by flow cytometry. Histograms show intracellular SAP protein (dark gray) in CD8⁺ T cells (upper histograms) and NK cells (lower histograms) in the mother and a brother of the patient (light gray histograms reflect isotype control or background staining). The mother demonstrates 2 populations with normal and absent SAP expression, respectively, reflective of her *SH2D1A* carrier status. The brother showed normal SAP expression, consistent with a normal *SH2D1A* gene. To compare, the typical pattern of absent SAP expression in an unrelated patient with XLP is shown on the right.

XLP is estimated to occur in 1 in 1 million males.² Reports suggest that more than 70% of affected males die by the age of 10 years, and, if they survive childhood, most die by the age of 40 years.^{1,2} Observed phenotypes in patients include fatal infectious mononucleosis (60%), malignant B-cell lymphomas (30%), dysgammaglobulinemia (30%), and aplastic anemia or vasculitides, which are associated with XLP (<3%).² Although the patient's clinical presentation was consistent with XLP, he was older than the widely reported typical age of presentation. This older age may reflect the demographics of primary EBV infection and its age-related symptoms, making the diagnosis of XLP additionally challenging in this patient. Primary EBV infection typically occurs in childhood and is

commonly asymptomatic. Infectious mononucleosis is characterized as a disease of affluent adolescents or young adults, and it is in this age range and demographic that symptoms occur.⁵ Because of the family's consent to an autopsy, sequence analysis of the *SH2D1A* gene could be performed on the patient's genomic DNA. The analysis revealed a previously reported nonsense mutation (Fig 1B⁶). Rapid testing by flow cytometry for SAP to evaluate protein levels could not be performed since viable lymphocytes are required; however, this analysis was performed on family members (Fig 1C⁷). The patient's mother and maternal grandmother were found to be carriers, and the patient's 2 brothers were negative for the mutation (Fig 1A). Based on the history, the maternal great-uncle who

died in childhood is presumed to have had XLP and died of complications of EBV.

Although the late age of 16 years at which complications of EBV in XLP were reported coupled with the fact that this was the age of primary EBV infection symptoms, maintaining a low threshold to evaluate for XLP was important in leading to the diagnosis. We suggest every child with severe liver dysfunction caused by EBV be assumed to have XLP, until proven otherwise. In early EBV infection of patients with known XLP, the use of rituximab has been effective and further emphasizes the need for rapid diagnosis.⁸ The rapid screening test for intracellular SAP should be performed and treatment with rituximab initiated. In this case, the important role of autopsy was demonstrated by allowing for definitive diagnosis and genetic counseling to evaluate all potential affected and carrier individuals for treatment or antenatal testing if indicated.

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